Review Article:
MANAGEMENT OF SUBCLINICAL VENTRICULAR DYSFUNCTION

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ABSTRACT

Sub Clinical Ventricular Dysfunction (SCVD) or Asymptomatic left ventricular dysfunction (ALVD) is a precursor of heart failure and cardiovascular deaths. Risk factors of progression of ALVD are elderly, male, coronary artery disease (CAD), hypertension and diabetes mellitus. Both ACE inhibitors and β-blockers could limit the progression of ALVD and reduced the risk of mortality and hospitalization. Roles of digoxin and aldosterone antagonists remained undefined in this population. Prophylactic therapy with implantable cardioverter defibrillator (ICD) could be reasonable in patients with post-myocardial infarction. Control of risk factors and comorbid conditions could slow down progression to overt heart failure. Therefore, early identification of ALVD through screening is of paramount importance.

Keywords: *Asymptomatic left ventricular dysfunction, ACE inhibitors, β-blockers*

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INTRODUCTION

Heart failure (HF) represents a contemporary health problem. In United States, it is estimated that 5 million people develop heart failure and there are 550,500 newly diagnosed patients annually. It results in mortality rate of 287, 200 individuals per year (an increase of 145% since 1979 through 1999) and a million of hospitalization and a total cost of USD 21.4 millions annually.[1-4] Study of the general population based on clinical criteria shows the prevalence of 0.3-2% and an increase of more than 10% for age above 65 year. Processes of heart failure is initiated by a wide variety of myocardial injuries, such as myocardial infarction, prolonged cardiovascular overload (hypertension, cardiac valvular disease), toxin (alcohol, cytotoxic medication), or infections (myocarditis, viruses) (Bernard 2006). As a consequence, there is a decrease in cardiac output and an increase in cardiac wall tension followed by dysfunction of baroreceptor that ends up with activation of some neuroendocrine systems, including renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (Francis et al 2008; Werner and Böhm 2008).

Heart failure is a wide spectrum of the left ventricular dysfunctions, from patients with normal size of left ventricles (LV) and ejection fraction (EF) to those with severe LV dilatation and decreased EF. In early phases, patients with systolic or diastolic left ventricular dysfunctions may be asymptomatic (Moukarbel and Solomon, 2008). The condition is known as Sub Clinical Ventricular Dysfunction (SCVD) or Asymptomatic Left Ventricular Dysfunction (ALVD). In the management of *The American College of Cardiology/American Heart Association (ACC/AHA) updates 2005* such a condition is classified as stage-B heart failure, representing a group of patients with structural heart diseases without the current or prior symptoms (Figure 1) (Moukarbel and Solomon, 2008; Hunt and Jessup 2009; Wang et al 2003).

Patients with stage-B LVSD are estimated to be four times higher in number than the combined stage-C and D patients. Increasing evidence indicates that the former group is at increased risk of developing morbidity and mortality and symptomatic HF. Despite the high risk, these patients are frequently undetected and untreated. Most patients with stage-B LVSD evaluated in clinical trials are related to ischemia, the rest being related to nonischemic causes such as hypertension, cardiac valvular diseases, cardiotoxin, post-viral infections/myocarditis, or familial idiopathic dilated cardiomyopathy.

Results of the large-scale randomized clinical trials with asymptomatic LVSD patients show that several pharmacological therapies can significantly reduce risks of the progression to symptomatic HF and mortality, including incidence of Sudden Cardiac Death (SCD). Additionally, Asymptomatic Left Ventricular Diastolic Dysfunction (ALVDD) is commonly found and related to a poor prognosis.[11] Nevertheless, there is currently no data on effectiveness of pre-symptomatic diastolic dysfunction treatment.

At High Risk of Heart Failure

Heart Failure

STAGE A

At high risk of HF but without structural heart diseases or symptoms of HF

STAGE B

Structural heart diseases but without signs or symptoms of HF

STAGE C

Structural heart diseases with prior or current symptoms of HF

STAGE D

Refractory HF requiring specialized interventions

e.g., Patients with:

- Hypertension
- Atherosclerotic disease
- Diabetes
- Obesity
- Metabolic syndrome

or

Patients

Structural heart disease

e.g., Patients with:

- Previous MI
- LV remodeling including LVH and low EF
- Asymptomatic vascular diseases

Development of symptoms of HF

e.g., Patients with:

- Known structural heart disease and
- Shortness of breath and fatigue, reduced exercise tolerance

Refractory symptoms of HF at rest

- e.g., Patients who have marked symptoms at rest despite maximal medical therapy (e,g., those who are recurrently hospitalized or cannot be safely discharged from hospital without specialized intervention)

THERAPY GOALS

- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- Control metabolic symptoms
  DRUGS

- ACEI or ABS in appropriate patients (see text) for vascular

THERAPY GOALS

- All measures under Stage A
  DRUGS

- ACEI or ARB in appropriate patients (see text)
- Beta-blockers in appropriate patients (see

THERAPY GOALS

- All measures under Stages A and B
- Dietary salt restriction
  DRUGS FOR ROUTINE USE

- Diuretics for fluid retention
- SCEI
- Beta blockers
  DRUGS IN SELECTED PATIENTS

- Aldosterone antagonist
- ARBs
- Digitalis
- Hydratazine nitrates
  DRUGS IN SELECTED PATIENTS

THERAPY GOALS

- Appropriate measures under Stages A, B, C
- Decision: appropriate level of care
  OPTIONS

- Compassionate end-of-life care hospice
- Extraordinary measures
  - heart transplant
  - chronic inotropes
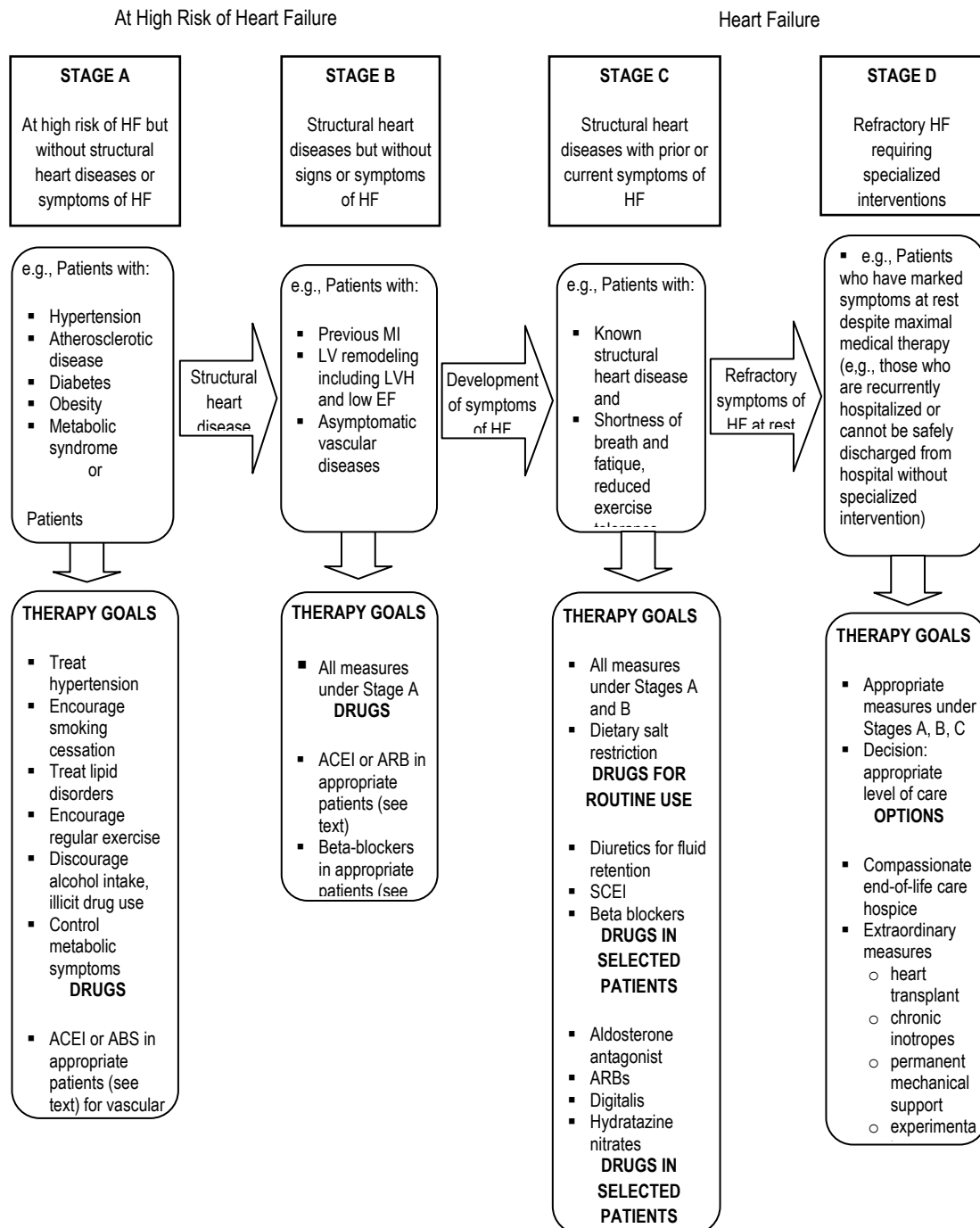 - permanent mechanical support
  - experimenta

Figure 1. Levels of progression of heart failure/therapeutic recommendations for individual levels. FHx CM, familial cardiomyopathic history; ACEI, angiotensin-converting enzyme inhibitors; ARB (Angiotensin Receptors Blocker) (Hunt and Jessup 2009)

PREVALENCE

Epidemiological identification of such patient group results in a considerable challenge due to the minimization and denial of the HF symptoms by the patients. Onset of the HF may be gradual and frequently unrealized by patients. Patients unconsciously reduce their daily activities to compensate for increasingly severe symptoms, thereby remaining free from symptoms. Hence, clinicians require objective examinations for distinguishing stage B and stage C.

A prevalence of SCVD or Asymptomatic Ventricular Dysfunction (AVD) is similar to that of heart failure or about 4% in population, particularly elderly group (Wang et al 2003; Albert and Lewis 2004). Community-based studies find that prevalence of Asymptomatic Left Ventricular Systolic Dysfunction (ALVSD) is within a range of 0,9%-12,9%. Three percent of the Framingham population (6% male and 0,8% female) have ejection fraction (EF) of less than 50% without HF signs (Goldberg and Jessup 2006; Moukarbel and Solomon 2008). Meanwhile, prevalence of ALVDD is unknown yet. Echocardiographic survey of the population indicates evidence of diastolic dysfunction in 27.4% of the subjects without heart failure (Moukarbel and Solomon 2008).

ETIOLOGY

Most LVSD cases occur gradually, initiated by all-cause myocardial injuries, especially acute infarction, and frequently exacerbated by hypertension and diabetes mellitus. Progression of coronary artery disease, diabetes mellitus, hypertension or onset of atrial fibrillation (AF) can accelerate a development of heart failure (Jessup et bal 2009). Loss of cardiac function initially results in activation of some compensatory mechanisms, such as peripheral vasoconstriction, saline and water retention, or increased non-infarcted myocardium contractility, in order to maintain the homeostasis of systemic blood flow and pressure. After a certain period of time, remodeling may occur in the forms of dilatation and hypertrophy of LV-space followed by myocardial fibrosis. This renders the LV to be more spherical with an increased end-diastolic volume, decreased systolic function (low LVEF), and decreased ventricular complaints. This remodeling process is partly mediated by neurohormones in sympathetic nervous system (norephinephrines, endothelins, vasopressins, and cytokines) and RAAS. The process can take place persistently in absence of the subsequent injuries

(Goldberg and Jessup 2006; Jessup et al 2009; Bernard 2006; Wang et al 2003; Albert and Lewis 2004)

According to *The Framingham Heart Study,* hypertension and coronary artery disease are the main etiology of heart failure in USA, representing over 80% of all HF cases in a 36-year follow-up. The study finds that 65% of patients with ALVSD have hypertensive history and 49% of them experience myocardial infarction. *The Epidemiologic Follow-up Study of the National Health and Nutrition Evaluation Survey (NHANES) I* show that more than 60% of the HF cases are caused by coronary artery disease. *The Studies of Left Ventricular Dysfunction (SOLVD) Prevention Trial* suggest that 83% of patients with ALVSD have CAD history and 37% have hypertension history.

Diabetes mellitus may play a role in the development of systolic dysfunction through structural and functional abnormalities related to enhanced fibrosis and irreversible collagen glycation. Additionally, diabetes can increase incidence of coronary atherosclerosis via fat metabolism and endothelial function. *The Epidemiologic Follow-up Study of (NHANES) I* reveals that physical inactivity, smoking, obesity, and cardiac valvular disease become independent risk factors for HF incidence.

MANAGEMENT

Clinicians are facing two principal challenges in management of the patient group: (1) management of complaints, (2) lack of evidence-based recommendations. Patients with ALVD may feel healthy and refuse to take medication for long period of time, especially in case of side-effects or additional expenses medical. In addition, supporting data on specific treatments were still limited. Therapeutic goal in this group is to reduce risk of further left ventricular damage and minimize a progression of the left ventricular dysfunction.

In addition to control of such risk factors as hypertension, diabetes mellitus, lipid abnormalities, smoking cessation, reduced alcohol consumption, some large-scale clinical randomized trials with patients with LVSD-related heart failure show that pharmacological treatment can improve outcome by suppressing neurohormonal system that may cause cardiac remodeling. Many patients in the study belong to stage B since LVSD is a primary determinant for inclusion irrespective of the presence of the HF symptoms. Review of these studies provides essential

insights into roles for medical therapies in patients with ALVSD.

Angiotensin-Converting Enzyme (ACE) Inhibitors.

Activation of RAAS in heart failure leads to formation of angiotensin II that will bind to AT I receptor and results in an increased peripheral resistance, myocardial hypertrophy, fibrosis, myocyte apoptosis, and oxidative stress (Opie et al 2005). Thus, it is rational to inhibit this RAAS early in order to prevent adverse effects on patients with heart failure or a group of patients with risk of heart failure using ACE inhibitors (Werner and Böhm 2008). The SOLVD *prevention trial* show that the use of enalapril in patients with ALVSD brings about a significant improvement in mortality and morbidity, both statistically and clinically (Wang et al 2003). In *The SAVE trial*, captopril administration to patients with post-myocardial infarction reduces 19% of all-cause deaths ($P < 0,019$), 22% of heart failure hospitalization ($P < 0,019$), and 36% of deaths due to heart failure deterioration ($P < 0,032$) (Wang et al 2003). *The Trandolapril Cardiac Evaluation (TRACE)* shows that administration of trandolapril reduces 30% of mortality risks in patients with ALVSD (Goldberg and Jessup 2006;[12])

β-Adrenergic Inhibitors.

In heart failure, the sympathetic nervous system is activated early, even long before the activation of RAAS. β-blockers can inhibit the sympathetic nervous system and β_1 receptor in renal juxtaglomerular cells, thereby reducing rennin secretion and eventually inhibits RAAS (Ponikowski 2006). Additionally, there are several action mechanisms of β-blocker beneficial to patients with heart failure: (1) normalization of calcium release channel, (2) improvement of β-adrenergic signaling, (3) protection of myocyte against toxic effects of catecholamines, (4) anti-arrhythmic effects, (5) heartbeat reduction, and (6) anti-apoptosis. Administration of β-blockers to patients with post-myocardial infarction can increase survival, decrease incidence of sudden death and reinfarction (Jessup et al 2009). There are some β-blockers usually used in patients with heart failure, namely carvedilol, metoprolol, and bisoprolol. Nevertheless, among those three, only carvedilol and metoprolol that are already examined for use in asymptomatic patients.

In *the SOLVD prevention trial* and *the SAVE trial*, administration of β-blockers in addition to ACE inhibitors in patients with ALVSD reduces mortality and hospitalization. In *the Australia-New Zealand heart failure trial*, administration of carvedilol indicates significant improvement of LVEF. In *the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial*, administration of carvedilol to stage-B patients reduces 31% of all-cause deaths. Echocardiographic studies indicate that carvedilol reduces LV volume and ameliorates LVEF. Effects of ACE inhibitors and β-blockers on cardiac remodeling are investigated in the *Carvedilol ACE Inhibitor Remodeling Mild CHF Evaluation (CARMEN)*. Administration of carvedilol decrease LV size and increase cardiac function. Patients treated with enalapril alone show no decrease in LV size and only minor improvement in LVEF. A study of the administration effects of ACE inhibitors or β-blockers alone, or in combination, on elderly patients with ALVSD indicates that combination therapy provides significant prevention of new coronary events and heart failure. In *the Reversal of Ventricular Remodeling with Toprol-XL (REVERT) trial*, administration of metropolol succinate to patients with ALVSD can stop and reverse remodeling (Moukarbel and Solomon 2008).

Angiotensin Receptor Blockers (ARB).

Inhibition of RAAS with ACE inhibitors apparently does not completely suppress the generation of angiotensin II. Thus, the use of ARB can improve outcome; nevertheless, accumulated evidence shows otherwise. In *the Valsartan in Acute Myocardial Infarction (VALIANT)*, administration of valsartan ameliorates mortality similar to captopril, and combination of both do not produce additional benefit but, instead, increase side-effects (hypotension, decrease in *glomeruluar filtration rate*) (Werner and Böhm 2008). In *the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL)*, administration of captopril provides a superior clinical outcome than losartan. There is no study supporting the combined use of ACE inhibitors and ARB in this population (Moukarbel and Solomon 2008). Recommendations for management of ACC/AHA suggest using ACE inhibitors as the first-line therapy and ARB as the second one in patients with intolerance to ACE inhibitors.

Digoxin.

In *the Digitalis Investigation Group (DIG) trial*, Administration of digoxin shows no improvement in mortality, but it reduces hospitalization and symptoms significantly. Since stage-B patients are asymptomatic, digoxin has no role in the population. In addition, digoxin is related to increased risks of arrhythmias and mortality.

Aldosterone Antagonists.

Role of aldosterone antagonists in patients with ALVSD has not been investigated yet. In the existant studies of *the Randomized Aldactone Evaluation Study (RALES) and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)*, the use of spironolactone and eplerenone demonstrates significant reductions in morbidity and mortality. However, these studies are conducted in a group of patients with symptomatic heart failure (stage C). There is no recommendation of ACC/AHA for the use of aldosterone antagonists in stage B patients.

Direct Renin Inhibitors.

As a new class of RAAS antagonists, direct rennin inhibitors provide a novel way to inhibit renin ability to convert angiotensinogen into angiotensin I. This offers an advantage of avoiding reflex in which levels of angiotensin I and II increase as in the case of administration of ACE inhibitors and ARB in order for the inhibitory potential to RAAS to be better and complete. Aliskiren is the first FDA-approved oral medication of this class for hypertension treatment. Whether this medication is potential to providing benefit to patients with ALVD is still under investigation (Moukarbel and Solomon 2008).

Non-Pharmacological Therapy.

Despite the fact that optimal pharmacological therapy can significantly reduce mortality risks, mortality rate remains high. For instance, survived patients with LVSD following myocardial infarction have four-to-five-year mortality rate of 20% and approximately 1/3 of which occur suddenly. This encourages investigation of a role of implantable cardioverter defibrillators (ICDs) as an adjunct therapy in HF patients with LVSD. In *the Multicentre Automatic Defibrillator Implantation Trial II (MADIT-II)* with post-MI patients, the ICD therapy reduces 31% of overall mortalities in comparison with the group with medical therapy alone.

In addition, patients with class I NYHA receive similar benefits as symptomatic patients. In *the Defibrillator in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study*, there is reduction in mortality at 35% in ICD group; however, only patients with class III NYHA obtain beneficial effect. These findings show that ICD therapy in patients with ALVSD is acceptable and should be taken into account in accordance with characteristics of individual patients (Moukarbel and Solomon 2008).

CONCLUSIONS

SCVD or ALVSD is a precursor of heart failure and cardiovascular deaths, representing a contemporary critical health problem. Elderly, male, coronary artery disease, hypertension and diabetes mellitus are risks factor for ALVSD progression. Both ACE inhibitors and *β*-blockers can prevent progression of ALVSD to heart failure and reduce risks of mortality and hospitalization. There is no place for use of digoxin and the role of aldosterone antagonists is still unknown. Prophylactic therapy with ICD may be useful in patients with post-myocardial infarction. Treatment of the underlying factor or comorbid factors such as hypertension and diabetes can slow down HF progression. Administration of appropriate therapy will improve outcome by reducing morbidity, mortality, and symptomatic HF progression.

REFERENCES

Bernard Silke. Beta-blockade in CHF: pathophysiological considerations. EHJ Supplements. 2006;8:C13-18.

Christian M. Werner, Michael Böhm. The therapeutic role of RAS blockade in chronic heart failure. Therapeutic Advances in Cardiovascular Disease. 2008;2(3):167-177.

Gary S. Francis, Edmund H. Sonnenblick, W. H. Wilson Tang, Philip Poole-Wilson. Pathophysiology of Heart Failure. In: Valentin Fuster, Robert A. O'Rourke, Richard A. Walsh, Philip Poole-Wilson, eds. Hurst's The Heart. 12nd ed. China: McGraw-Hill; 2008. p.691-712.

George V. Moukarbel, Scott D. Solomon. Treatment of Asymptomatic Left Ventricular Dysfunction. Current Treatment Options in Cardiovascular Medicine. 2008;10:476-485.

Kenneth Dickstein, Alain Cohen-Solal, Gerasimos Filippatos, John J. V. McMurray, Piotr Ponikowski, Philip Alexander Poole-Wilson, et al. Diagnosis and Treatment of Acute and Chronic Heart Failure 2008. In: Alec Vahanian, John Camm, Raffaele De Caterina, Veronica Dean, Kenneth Dickstein, Gerasimos Filippatos, et al, eds. ESC Guidelines Desk Reference. London: Lippincott Williams & Wilkins; 2008. p.313-338.

Lee R. Goldberg, Mariell Jessup. Stage B Heart Failure, Management of Asymptomatic Left Ventricular Systolic Dysfunction. Circulation. 2006;113:2851-2860.

Lionel H. Opie, Philip A. Poole-Wilson, Marc A. Pfeffer. Angiotensin-Converting Enzyms (ACE) Inhibitors, Angiotensin-II Receptor Blockers (ARBs), and Aldosterone Antagonists. In: Lionel H. Opie,

Bernard J. Gersh, eds. Drugs for the Heart. 6th ed. Philadelphia: Saunders Elsevier; 2005. p.104-148.

M. Jessup, William T. Abraham, Donald E. Casey, Arthrur M. Feldman, Gary S. Francis, Theodore G. Ganiats, et al. 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. Circulation. 2009;119:e391-e479.

Michael R. Zile. Treatment and prognosis of diastolic heart failure. Available from: URL:http://www.uptodate.com

Nancy M. Albert, Connie Lewis. Recognizing and Managing Asymptomatic Left Ventricular Dysfunction After Myocardial Infarction. Critical Care Nurse. 2004;24:14-29.

Piotr Ponikowski. Rationale and design of CIBIS III. EHJ Supplements. 2006;C:C35-C42

Rainer Dietz. Current implementation of proven therapy in heart failure. EHJ Supplements. 2004;6:H43-8.

Sharon A. Hunt, Mariell Jessup. Heart Failure. In: Valentin Fuster, ed. The AHA Guidelines and Scientific Statements Handbook.1st ed. Dallas: Blackwell Publishing; 2009. p.223-235.

Thomas J. Wang, Daniel Levy, Emelia J. Benjamin, Ramachandran S. Vasan. The Epidemiology of 'Asymptomatic' Left Ventricular Systolic Dysfunction: Implications for Screening. Ann Intern Med. 2003;138:907-916.

Wilson S. Colucci. Evaluation and management of asymptomatic left ventricular systolic dysfunction. Available from: URL:http://www.uptodate.com

Wilson S. Colucci. Screening for asymptomatic left ventricular dysfunction. Available from: URL:http://www.uptodate.com